PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference W5-208003PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/002379	International filing date *(day/month/year)* 07.03.2005	Priority date *(day/month/year)* 05.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/4453 A61P25/02 A61K9/22 A61K9/26 A61K47/32		
Applicant SANOCHEMIA PHARMAZEUTIKA AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.09.2005	16.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hornich, E Telephone No. +49 89 2399-8721

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002379

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-21 as originally filed

   Claims, Numbers

   1-22 received on 24.12.2005 with letter of 21.12.2005

   Drawings, Sheets

   1-5 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 23-69
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1 (see separate sheet)
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

SECTION I

1. **Art. 34(2)(b) PCT**

According to claim 1, the controlled release agent may be selected from Eudragit RS, Eudragit L, Eudragit S.

According to the application documents as originally filed (description and claims), the controlled release agent may be a ***mixture*** of Eudragit RS, Eudragit L and Eudragit S.

The use of the individual compounds separately is not disclosed in the application.

The afore-mentioned amendment of claim 1 thus violates the requirements of **Art. 34(2)(b) PCT**.

SECTION V

2. *References*:

D1: WO 00/59508 A
D2: US-A-4 702 918
D3: US 2002/119197 A1
D4: EP1101490
D5: EP-A-1 238 662
D6: EP-A-1 252 887
D7: WO 02/060415 A
D8: YOKOYAMA ET AL: "Determination of tolperisone enantiomers in plasma and their disposition in rats" 1992, STN CHEMICAL ABSTRACTS

3. *Novelty* (**Art. 33(2) PCT**) with regard to *item 1*.

3.1 None of the available prior art documents discloses a controlled release pharmaceutical

composition of tolperisone as defined in the present claims 1, 16 or 18, were Eudragits are used as controlled release agent in the core and the coating.

3.2 The following documents are mentioned in particular:

D1 discloses various pharmaceutical delayed release compositions for oral delivery of tolperisone. The isomeric ratio of tolperisone may be varying; 50/50 racemates are for instance used.
D1 does not disclose coated tablets. Eudragits are also not mentioned as controlled release agents or coating materials.

D1 does not anticipate the subject-matter of the present claims.

D3 discloses controlled release compositions of active agents. Tolperisone is mentioned within the listed active agents. The pharmaceutically active agent is dispersed in the core in a matrix material (for instance polymethacrylates). The core is surrounded by a coat. Eudragit RS is disclosed as a suitable coating material.

D3 does not anticipate the subject-matter of the present claims. **D3** does not disclose the pharmaceutical composition defined in the present claims, comprising tolperisone in the defined amount and the particular Eudragits as mentioned in the claim.
In the examples, Eudragit RS is used as a coating material, the core material however is not an Eudragit.

D4 discloses a controlled-release composition comprising a core material which comprises an active agent, the core being coated with a mixed film of a hydrophobic organic compound and an enteric polymer.
The active agent may be *tolperisone*, selected from a list of active agents; the enteric polymers may be enteric acrylic copolymers, e.g. Eudragits (L, S, RS).
Eudragit is however not mentioned as a core material. Thus, different polymeric compounds for the core layer and for the coating layer are proposed. No amounts are mentioned for tolperisone.

D4 does not anticipate the subject-matter of the present claims.

D5,**D6** or **D7** also relate to sustained-release compositions of e.g. tolperisone, selected from a list of active agents. The coatings may comprise various Eudragits.
However, **D5** to **D7** do not disclose the pharmaceutical composition defined in the present claims, comprising tolperisone in the defined amount and the particular Eudragits as mentioned in the claim.

D5: The core comprises no binder, or only small amounts of a binder, which is however not Eudragit.
D6: Sustained release preparation having a drug core coated with layers of various hydrophobic organic compounds and water soluble polymers. Eudragits are not mentioned as core materials.
D7discloses a multiparticulate pharmaceutical, comprising at least two different forms of pellets, the core of which contains a pharmaceutical agent with different polymer coatings. Both of the inner and outer coating of the pellet form A may be composed of Eudragits.

3.3 The present claims appear therefore novel.

4. *Inventive Step* (**Art. 33(3) PCT**) with regard to *item 1*.

The problem to be solved in the present application is to formulate an orally administrable, controlled release pharmaceutical composition of tolperisone, by means of which the in-vivo inversion of tolperisone is influenced.

The solution of the present application resides in a controlled release pharmaceutical composition according to claims 1, 16 or 18.

From the prior art documents **D1** or **D8** it is known that tolperisone is inverted in-vivo.

The available prior art does not suggest a composition according to the present claims

1, 16 or 18. Eudragits are mentioned in the prior art documents as suitable controlled release coating agents; however, Eudragits as polymer matrix for cores comprising tolperisone are not disclosed.

Thus, the use of Eudragits in the core as well as in the coating in pharmaceutical compositions of tolperisone is not suggested by the prior art.

For the examples 1 and 3, it is shown that the formulations result in a higher amount of (-)-R-tolperisone than (-)-R-tolperisone (see fig. 3, AUC data). The plasma area under the curve (AUC) concentration ratio of R-tolperisone to S-tolperisone is higher than 3:1. The AUC ratio of R-tolperisone to S-tolperisone of the formulation 'state of the art' (see example 9 and fig. 3) is lower.

Thus, although the in-vivo inversion is known from the prior art, the extent of this inversion apparently depends from the release of tolperisone.

It appears therefore that the problem underlying the present application has been solved. An inventive step can therefore be acknowledged for the subject-matter of the present claims.

5. *Industrial Applicability* **(Art. 33(4) PCT)**

The requirements of industrial applicability are fulfilled for the subject-matter of claims 1-22.